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Original Article

Predictive value of plasma D-Dimer and fibrinogen degradation products on prognosis of acute coronary syndrome

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Abstract: Objective: To investigate the clinical value of combined detection of plasma D-Dimer and fibrinogen degradation products (FDP) on predicting the prognosis of patients with acute coronary syndrome (ACS). Methods: 126 patients confirmed of ACS at our hospital were selected in this study, and divided into two groups-observation group (68 cases, with MACE) and control group (58 cases, without MACE), according to the occurrence of major adverse cardiovascular events (MACE). The levels of D-Dimer, FDP, PT, INR and PLT were detected and compared between the two groups. The patients were followed-up for 1 year, and the occurrence of MACE in two groups was recorded. Logistic regression analysis was used to analyze the risk factors for the occurrence of MACE in ACS patients. ROC curve was used to evaluate the best cutoff points of D-Dimer and FDP to predict MACE in ACS patients. Results: The plasma levels of D-Dimer and FDP in observation group were obviously higher than those in control group (t=3.175, 3.629, $P < 0.05$), however, the differences in the indices of PLT, PT and INR were not statistically significant between two groups ($P > 0.05$). The plasma levels of D-Dimer and FDP were confirmed to be the risk factors for the occurrence of MACE by multivariate logistic regression analysis. The area under ROC curve for D-Dimer and FDP alone in predicting MACE for ACE patients was 0.796 and 0.682 respectively (P=0.014, 0.028). But, with the cut-off point of 0.64 mg/L for D-Dimer and 2.26 μg/L for FDP, the AUC of combined prediction of D-Dimer and FDP was 0.857, and the sensitivity, specificity and accuracy for the prediction were 46.6%, 78.3% and 56.8%, respectively. Conclusion: The combined detection of plasma D-Dimer and FDP has good predictive value for the occurrence of MACE in patients with ACS.

Keywords: Acute coronary syndrome, D-Dimer, fibrinogen degradation product, major adverse cardiovascular events, predictive value

Introduction

Acute coronary syndrome (ACS) is one of the common clinical emergency diseases that seriously threats people's health worldwide. Recently in China, with the economic development, lifestyle change and high incidence of chronic diseases such as diabetes and hypertension etc, the morbidity and mortality rates of ACS are increasing, thus, ACS has become a serious public health event that attracts a lot of attention [1]. ACS is a severe type of coronary heart disease, and its pathophysiological basis is the instability of coronary atherosclerosis plaque, which is easily to rupture that may induce platelet aggregation and lead to complete or incomplete coronary artery embolism, and further causes severe lumen stenosis and myocardial blood supply shortage [2]. At present, the treatment principle of ACS is early detection, early diagnosis and early treatment to achieve revascularization. In recent years, with the development in Chest Pain Center and interventional technology, ACS patients can receive timely treatment to accomplish revascularization [3], however, research has found that some ACS patients would still develop major adverse cardiovascular events (MACEs) even after getting through the acute phase; MACEs can cause serious threats to the quality of life and even lead to death of patients. Therefore, predicting the short-term prognosis

Table 1. Comparison of the basic information between two groups of patients

Group	Age (years)	Sex ratio (male:female)	Body mass index (kg/m^2)	History of hypertension (%)	History of hyperlipidemia (%)	History of diabetes (%)
Control group	60.3 ± 7.0	35:23	19.3 ± 2.7	58.6 (34/58)	37.9 (22/58)	32.8 (19/58)
Observation group	57.5 ± 5.8	40:28	20.1 ± 3.0	60.3 (41/68)	38.2 (26/68)	35.3 (24/68)
t/χ^2 value	1.878	6.735	2.020	6.515	6.712	6.871
P value	0.071	0.060	0.062	0.069	0.062	0.055

for ACS patients is one of the hot issues that draw clinical attention [4]. The pathological basis of ACS is thrombosis caused by abnormal fibrinolysis and blood coagulation, and the pathological basis of MACE is the formation of sub-acute or chronic coronary embolism [5]. In recent years, the researches confirmed that there was a correlation between the prognosis of patients with ACS and diverse biochemical markers, including homocysteine (Hcy), N terminal pro-plasma B natriuretic peptide (NT-pro BNP), oxidized low density lipoprotein (ox-LDL), troponin t (TNT), C-reactive protein (CRP), etc. However, clinical practice also showed that the sensitivity and specificity of these biomarkers were difficult to meet the clinical requirements. So, their clinical application value is limited [2]. The current study start to pay attention to D-Dimer and fibrinogen degradation product (FDP), and most researchers believe that D-Dimer or FDP can not only reflect the coagulation function of the body, but also reflect the fibrinolytic activity [6]. At present, some clinical studies have analyzed the correlation between D-Dimer or FDP level and the short-term prognosis of patients with ACS, but the sensitivity of predicting the outcome of ACS patients by detecting individual indicator was poor [4]. Therefore, this study examined both D-Dimer and FDP together to predict the short-term prognosis of ACS patients.

Material and methods

Study subject

126 cases of ACS patients treated in our hospital from January 2014 to December 2015 were selected in this study. The patients consisted of 75 males and 51 females, aged from 54 to 69 years old with an average of (58.6 ± 6.8) years old; there were 49 cases of ST elevation acute myocardial infarction, 18 cases of non-ST elevation acute myocardial infarction, and 59 cases of unstable angina. All patients signed informed consent.

Inclusion criteria: (1) patients were diagnosed of ACS according to *Guidelines for the diagnosis and treatment of coronary heart disease* established by Cadiovascular Branch of Chinese Medical Association; (2) patients could adhere to regular follow-up, and with complete clinical treatment data; (3) ≤ 70 years old.

Exclusion criteria: (1) patients underwent thrombolysis and interventional therapy in the past 6 months; (2) patients with cerebral infarction or cerebral infarction accompanied with hemorrhage in the past; (3) patients with severe cardiac tamponade, ventricular arrhythmias, cardiac shock and other diseases; (4) patients with severe lung, liver, kidney and other important organ dysfunction.

Grouping

All patients were divided into two groups according to the outcome of 1 year follow-up: control group, a total of 58 cases without MACE, including 35 males and 23 females, mean age was (60.3 ± 7.0) years old; Observation group, a total of 68 cases with MACE, including 40 males and 28 females, mean age was (57.5 ± 5.8) years old. There were no significant differences in age, sex ratio, body mass index and disease history as well as other clinical factors between the two groups (P > 0.05) (as shown in **Table 1**).

Laboratory parameters

5 ml fasting venous blood was drawn from all patients and centrifugated at 3000 r/min for 10 minutes, the plasma was separated and stored in -70°C environment. ELISA (Elecsys 2010 type, purchased from Roch, USA) was used to detect the plasma D-Dimer concentration in each sample with double-antibody sandwich technique. At the same time, automatic blood coagulation instrument was used to detect FDP, prothrombin time (PT), international normalized ratio (INR levels) of each blood sample, and the platelet count (PLT) was also recorded.

Table 2. Comparison of plasma levels of each index between two groups of patients

Group	Number of cases	D-Dimer (mg/L)	FDP (μg/L)	PLT ($\times 10^9$/L)	PT (s)	INR
Control group	58	0.24 ± 0.13	1.87 ± 0.26	17.9 ± 3.0	13.5 ± 1.6	1.17 ± 0.21
Observation group	68	0.88 ± 0.19	3.96 ± 0.34	15.3 ± 2.2	14.1 ± 1.3	1.29 ± 0.32
T value		3.629	3.175	2.208	2.114	2.161
P value		0.006	0.013	0.057	0.071	0.062

Table 3. Multivariate logistic regression analysis for the occurrence of MACE in ACS patients

Clinical indicators	β	SE	Wald x^2 value	OR (95% CI)	*P* value
D-Dimer	2.246	0.006	8.752	9.456 (4.867, 12.106)	0.009
FDP	1.475	0.014	6.354	4.371 (2.901, 9.365)	0.033
PLT	0.031	0.241	4.632	1.032 (0.598, 1.927)	0.092
PT	0.196	0.183	5.809	1.217 (0.423, 2.142)	0.083
INR	0.387	0.060	4.778	1.473 (0.866, 2.112)	0.072

MACE records

Patients of both groups were followed up for 1 year with an interval of 3 months after discharging from hospital. The number and type of MACE occurred to each patient was carefully recorded. MACE was defined as: cardiac death, nonfatal myocardial infarction, target vessel revascularization.

Statistical method

SPSS 17.0 software was used for statistical analysis; measurement data was expressed as mean ± standard deviation, and *t* test was used for the comparison between the two groups; count data was expressed as percentage, and χ^2 test was used for the comparison between the groups. The risk factors for MACE during the follow-up was analyzed by multi-factor logistic regression; ROC curve of plasma D-Dimer and FDP in diagnosing MACE for ACS patients was drawn, and the diagnostic cut-off value was calculated, as well as the sensitivity and specificity. $P < 0.05$ was considered statistically significant.

Results

The comparison of plasma indices between two groups

Plasma levels of D-Dimer and FDP of observation group were significantly higher than those of control group (D-Dimer: (0.88 ± 0.19) mg/L *vs.* (0.24 ± 0.13) mg/L; FDP: (3.96 ± 0.34) μg/L *vs.* (1.87 ± 0.26) μg/L) (all $P < 0.05$). However, the plasma contents of PLT, PT and INR of two groups were not statistically different ($P > 0.05$) (**Table 2**).

Multivariate Logistic regression analysis

The occurrence of MACE was regarded as dependent variable, while plasma D-Dimer, FDP, PLT, PT and INR levels were regarded as independent variables, and the results showed that plasma D-Dimer and FDP were the risk factors for the occurrence of MACE in ACS patients ($P < 0.05$), while the others were not ($P > 0.05$) (**Table 3**).

Predictive value of D-Dimer and FDP on the occurrence of MACE in ACS patients

The area under ROC curve (AUC) of D-Dimer and FDP for predicting the occurrence of MACE in ACS patients was 0.796 and 0.682, respectively (P=0.014, 0.028) (see **Table 4**; **Figure 1**). But, with the cut-off point of 0.64 mg/L for D-Dimer and 2.26 μg/L for FDP, the AUC of combined prediction of D-Dimer and FDP was 0.857, and the sensitivity, specificity and accuracy for the prediction were 46.6%, 78.3% and 56.8%, respectively.

Discussion

With the accelerated speed of aging society in China and the high incidence of hypertension, diabetes and other chronic diseases, the incidence of ACS in China has maintained a high level. Although the results of numerous clinical trials in recent years have greatly promoted the progress of the treatment of ACS, the clinical epidemiological survey showed that the incidence of MACE in ACS patients during the 1 year follow-up is still not ideal [2, 5]. At present, it is generally accepted that the major measure

Table 4. Predictive value of D-Dimer and FDP on the occurrence of MACE in ACE patients

Detection index	AUC	Best cut off value	Sensitivity (%)	Specificity (%)	Accuracy (%)	*P* value
D-Dimer	0.796	0.64 (mg/L)	59.4	61.5	46.9	0.024
FDP	0.682	2.26 (μg/L)	73.8	35.7	50.3	0.011
FDP-D-Dimer	0.857		43.8	75.2	57.4	0.026

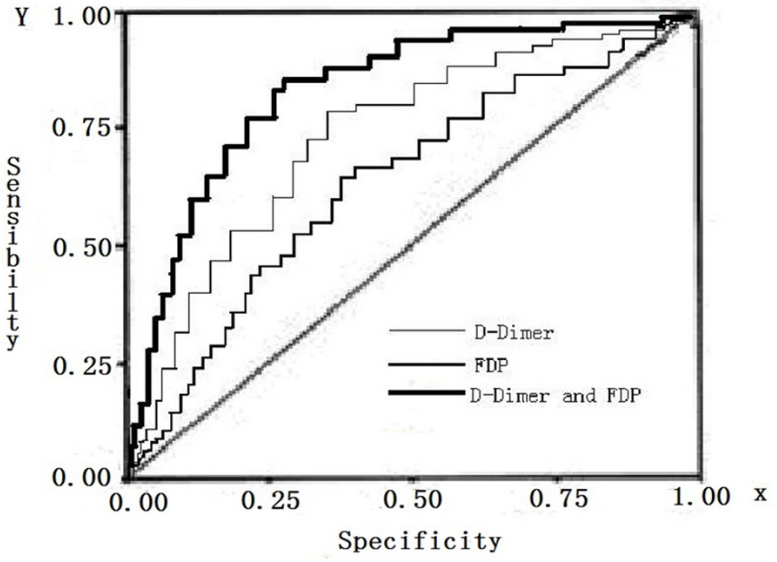

Figure 1. ROC curve of D-Dimer and FDP in predicting the occurrence of MACE in ACE patients.

to improve short-term prognosis of ACS patients is to more accurately assess the risk population and early intervene [6]. There have been many clinical researches on the predictive value of NT-proBNP, C-reactive protein, ox-LDL and other markers on the short-term prognosis for ACS patients [2, 7, 8] and clinical practice showed un-ideal outcomes in both sensitivity and specificity; now, there is still a lack of suitable indices to predict the probability of MACE in ACS patients in short period and to evaluate the prognosis of ACS patients.

Pathophysiology studies showed that, the pathological basis of ACS is a series of blood coagulation and fibrinolytic response caused by plasminogen system, which activated by unstable rupture of coronary atherosclerotic plaque, and all of these eventually lead to coronary thrombus and vascular obstruction [9]. Clinic outcomes also confirmed that the incidence of ACS is related to thrombosis, severe progressive coronary artery occlusion, coronary spasm and contraction, excessive immune inflammation, and elevated myocardial oxygen consumption etc. [10]. Under normal physiological status, coagulation system and fibrinolytic system keep a dynamic balance in coronary artery; however, the blood of ACS patients is at hypercoagulable state with high blood viscosity, and many contents in blood interact with impaired coronary wall, leading to thrombus formation and finally representing acute myocardial infarction and other coronary events [11]. The study showed that the plasma D-Dimer, FDP, fibrinogen and other markers were positively correlated with the activity of coagulation and fibrinolysis system, the plasma level of these indicators increased significantly as the coronary artery lesions worsened [12].

D-Dimer is the specific degradation product of the cross linked fibrin after activated by fibrinolytic system. Its immunocompetence fragment can reflect the plasma concentration of cross-linked fibrin polymer, and its plasma level can effectively and specifically reflect the increase in blood circulating coagulation and the level of secondary fibrinolytic hyperactivity; the higher plasma D-Dimer level indicates the higher degree of formation and dissolution of fibrin in body [13, 14]. In recent years, some studies showed that high plasma D-dimer levels would activate monocyte to release interleukin 6 (IL-6), so it has been regarded as the high risk factor for coronary event [15]. FDP is the overall degradation products of fibrinogen or fibrin that under the action of plasmin. Its plasma level not only indirectly reflects the activity of fibrinolytic enzyme, but also indicates the thrombus condition [16]. A number of studies indicated that increased plasma fibrinogen level is an independent risk factor for coronary artery disease and other arterial thrombosis complications [17]. In recent years,

a number of abroad clinical studies confirmed that plasma D-Dimer, fibrinogen and plasminogen significantly increased with the increasing in severity of coronary artery disease [18, 19]. In recent years, a number of clinical studies have shown that FDP and D-dimer are related to the occurrence of MACE in ACS patients [20-22], however, most of these studies only checked FDP or D-dimer individually, some other studies checked the FDP or D-dimer combined with other markers, and those clinical outcomes showed limited value in the prediction of short-term prognosis for ACS patients. Therefore, we evaluated the plasma levels of both FDP and D-Dimer of ACS patients to evaluate their short-term prognosis.

The result of present study showed that the plasma levels of FDP and D-Dimer in ACE patients with MACE were significantly higher than those without MACE, indicating a correlation between the occurrence of MACE and plasma levels of FDP and D-Dimer. Multivariate logistic regression analysis showed that plasma FDP and D-Dimer were the independent risk factors for the occurrence of MACE in ACE patients. Further analysis of the predictive value of plasma FDP and D-Dimer showed that FDP or D-Dimer alone was not ideal in the accuracy of evaluating MACE incidence for ACE patients, but the combined detection could realize a better prediction with D-Dimer ≥ 0.64 mg/L and FDP ≥ 2.26 μg/L. Therefore, combined detection of plasma FDP and D-Dimer can well forecast the possibility of MACE in ACE patients. However, due to the small samples included in this study and the short follow-up period, the results of this study still need to be validated by long-term clinical trials of multiple centers.

Disclosure of conflict of interest

None.

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